PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Insight into Hepatitis B Prevalence and Risk Factors Among Vietnamese Americans: An Analysis of Data from a Community-Based Screening Program
AUTHORS	Lee, Alice; Jacobs, Wura; Chan, Elena; Nguyen, Becky; Hua, Dung; Ho, John; Yuen, Priscilla; Van Nguyen, Thai

VERSION 1 – REVIEW

REVIEWER	Thi T. Hang Pham Stanford University School of Medicine USA
REVIEW RETURNED	26-Mar-2019

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript. The aims of this study are important and results are very useful to inform future interventions that target Vietnamese Americans to reduce HBV related burden. Overall: - I am concerned that ethics approval was not mentioned. Did the study obtain ethical approval from any institution before the implementation? - It looks like the study collect identifiable data from all participants. Was informed consent obtained from study participants at the time of interviewing and testing? If so, is it verbal or written consent? - It will be useful to include the survey questionnaire as an appendix - Citation: The punctuation for the sentence should go AFTER the parenthesis. Please check. Introduction: - Data used in the 1st sentence of the first paragraph was out of date (2006). Please use more recent data, for example, in 2018 WHO estimated 257 million people are living with hepatitis B virus infection https://www.who.int/news-room/fact-sheets/detail/hepatitis-b Methods: Study Population: - Please elaborate why this was a cross-sectional study. It is tricky to justify the sample size and sample selection methods because data was from community events that provide free HBV testing to attendees. It may be easier to describe the study as an analysis of data from a community-based intervention program by The Vietnamese American Cancer Foundation. - Please clarify the deduplication methods used to exclude

	those who participated in multiple events. Was a unique identifier assigned for each individual and how? For those individuals, what data was used for analysis? Were the most recent test results used? Data Ascertainment: - Not clear if the questionnaire is self-administrated or attendees were interviewed by the trained staff. Please elaborate. - Please specify what risk factors and HBV knowledge questions were included in the questionnaire. It was mentioned that a 30-minute lecture on hepatitis B was given at the event. Would this affect how participants respond to the questionnaire in term of their HBV knowledge? - How many (%) of participants participated in follow-up events to receive testing results and how many (%) received results via mail? - The last sentence stated: “Staff also contacted these individuals to ensure they received proper follow-up care if needed”. Is follow-up data for those who tested positive available? How many tested positive, how many reached, how many received follow up care?. If available, it will be very interesting to include this cascade information in the MS. - Please elaborate data management procedure (how data stored and managed) Statistical Analysis: - Please include reference(s) for choosing p-value cut off point <= 0.10 for inclusion in multivariate logistic regression. - Can you explain why year of screening was factored in multivariate analysis (Table 3)? Did the data analysis detect any differences in outcomes by year of screening? Results: - The first sentence of the second paragraph cited Table 2. However, Table 2 seem not have this information. Please add a TOTAL column to table 2 to illustrate information in this sentence. Discussion: - Discussion was made closely linked to findings of this study and elaborated according to stratification of results - In many cases, attendees of health fairs/events that offer free tests are from low-income and uninsured families and not necessarily a representative sample of the population of interest. A comparison of the study participants’ characteristics with available data on the Vietnamese Americans population will be helpful (e.g. family income, education, place of birth (foreign/US born).

REVIEWER	Michael Vinikoor University of Alabama at Birmingham, USA
REVIEW RETURNED	05-Apr-2019

GENERAL COMMENTS	Overall This paper described serological tests from several thousand people of Vietnamese origin in Southern California and >95% of them were immigrants and >90% of them were older than 40 years old. While, it is nice to spread the word that this group has high HBsAg-positivity, this paper is not likely to have a broad appeal because of its limited population and limited data reported here. I wish data were available on what happened to those with positive results on HBsAg. Finding HBsAg-positive immigrants and linking them to anti-HBV drugs to reduce the incidence of cancer is a major priority in the NIH viral hepatitis action plan. Perhaps the authors could frame the paper as

	implementation science, esp. if they have data on the events themselves (how many came, what % took a test, got results, where was this doctor visit with results, who went for follow-up and where). That would have more public health impact and would provide rationale for more resources spent testing and linking to care in this community. Intro • In paragraph 3, when you say Vietnamese American do you mean foreign-born or immigrants? When you say no change over the past 3 decades… are you implying that the # of imported cases of HBV have been stable or are you saying there is transmission on US soil? Why would the incidence of liver CA be expected to drop if there is stable immigration of HBsAg-positives? In fact, if the number immigrating increases, wouldn't the incidence of liver CA in people of Vietnamese ethnicity be possibly increasing? • What else makes Vietnam or vietnames unique in terms of HBV. Are HBV control policies different in Vietnam? Are there cultural practices that promote transmission or prevent prevention? Can you make the case better for such a limited study on this group? Do interventions to test and treat HBV in V.A.s need to be different from other Asian immigrant groups? • What do you mean 'updated evaluation?' Was there another identical serosurvey 10 years ago that you repeated? Methods • State the size of the Vietnamese community in the counties where the community events occurred so we can know what % more or less were reached. • Where did the testing events occur? Churches? Etc. • What do you mean complete results? I would not exclude those who at minimum have HBsAg test results. • Ethical considerations such as approval to use the data for research are not mentioned. • What assays were used for the HBV serologies as some of the tests are not as accurate and this would reduce confidence in results. Results • How many events occurred? How many were tested per event? • Better to say in the results the specific factor. Such as men had increased odds (P=XXX) than just mentioning gender as being associated. • In the text, don't give both bivariable and multivariable analysis. Just multi- • What happened to the HBsAg-positives? Were these new diagnoses? Were they linked to care and treatment? Were they screened for cancer? Did you do index testing where their first degree relatives and partners were also tested? • Did you vaccinate those who were non-immune? • How many did not come for results? How many had to be mailed out? Discussion • Gender differences in HBsAg-positivity are likely due to natural history of virus and host immunity (estrogens, etc.). • Would be great to talk about the fairs more as an intervention. What made them succeed? What could make them better? How to link patients to care if they are found HBsAg-pos?

	• How do we use these data to find HBsAg-pos in America? • How should the results on the 'factors associated with HBV' be used?

VERSION 1 – AUTHOR RESPONSE

Reviewer #1:

Overall Comment #1: "I am concerned that ethics approval was not mentioned. Did the study obtain ethical approval from any Institution before the implementation?"
Response: We did obtain institutional ethics committee approval from California State University, Fullerton prior to analyzing the data presented in this manuscript. We had originally included this information after the manuscript, but we should have also mentioned it within the manuscript, which we have now done. The following statement can be found at the end of Data Ascertainment in the Methods of our revised manuscript: "The data analyzed in this report had institutional ethics committee approval from California State University, Fullerton".

Overall Comment #2: "It looks like the study collect identifiable data from all participants. Was informed consent obtained from study participants at the time of interviewing and testing? If so, is it verbal or written consent?"
Response: Consent was obtained from study participants at the time the questionnaire was administered. The consent was written. We have included this information in the revised manuscript.

Overall Comment #3: "It will be useful to include the survey questionnaire as an appendix".
Response: Although the survey questions used in this analysis remained unchanged, the Vietnamese American Cancer Foundation (VACF) did have multiple versions of their questionnaire to reflect changes in their target population's needs and the agency's assessment needs over time. Therefore, instead of including the questionnaire(s) in the appendix, we believe it would be appropriate if interested readers directly requested this from us if they need it.

Overall Comment #4: "Citation: The punctuation for the sentence should go AFTER the parenthesis. Please check."
Response: We did not find any citation instructions in the journal's submission guidelines. However, we will fix our citation formatting if the journal asks us to.

Introduction Comment #1: "Data used in the 1st sentence of the first paragraph was out of date (2006). Please use more recent data, for example, in 2018 WHO estimated 257 million people are living with hepatitis B virus infection."
Response: We have revised the manuscript to reflect the more recent hepatitis B prevalence data from the WHO per the reviewer's suggestion.

Methods Study Population Comment #1: "Please elaborate why this was a cross-sectional study. It is tricky to justify the sample size and sample selection methods because data was from community events that provide free HBV testing to attendees. It may be easier to describe the study as an analysis of data from a community-based intervention program by The Vietnamese American Cancer Foundation."
Response: We agree with the reviewer's suggestion that it may be easier to describe the study as an analysis of data. Hence, we have revised the manuscript's title to the following: "Insight into Hepatitis B Prevalence and Risk Factors Among Vietnamese Americans: An Analysis of Data from a Community-Based Screening Program". We have also revised the abstract from "Design: Cross-

sectional study" to "Design: Analysis of data from a community-based screening program" and the first sentence of the Methods from "This cross-sectional study" to "This analysis".

Methods Study Population Comment #2: Please clarify the deduplication methods used to exclude those who participated in multiple events. Was a unique identifier assigned for each individual and how? For those individuals, what data was used for analysis? Were the most recent test results used?
Response: VACF only assigned a unique identifying number for each screened participant at each event. They did not assign a unique identifying number for each individual across all events. Therefore, we assumed participants of the same sex and date of birth were duplicates and excluded them from the analysis. In other words, our current analysis pools individuals who participated in only one screening event. We have clarified this in our revised manuscript.

Methods Data Ascertainment Comment #1: Not clear if the questionnaire is self-administrated or attendees were interviewed by the trained staff. Please elaborate.
Response: The questionnaire was self-administered. However, trained staff were present to answer questions. We have clarified this in our revised manuscript.

Methods Data Ascertainment Comment #2: Please specify what risk factors and HBV knowledge questions were included in the questionnaire. It was mentioned that a 30-minute lecture on hepatitis B was given at the event. Would this affect how participants respond to the questionnaire in term of their HBV knowledge?
Response: We have revised the manuscript to specify the information that was collected from the participants in the questionnaire. This included demographics, family history of hepatitis, hepatitis B vaccination status, and knowledge of one's own hepatitis infection status as well as the infection statuses of household members. With regards to the 30-minute lecture on hepatitis B, participants attended this lecture after completing the questionnaire so this would not affect the participants' responses on the questionnaire. Also, the questionnaire did not assess participants' knowledge and understanding of hepatitis B. We realize this was unclear in our manuscript and have revised it accordingly.

Methods Data Ascertainment Comment #3: How many (%) of participants participated in follow-up events to receive testing results and how many (%) received results via mail?
Response: VACF only organized follow-up events for their biannual screening events. They estimate approximately 50-60% of screened participants attended the follow-up events to receive their results. The other 40-50% receive their results via mail. For the other community health fair and events in which VACF provided screening services, all participants received their results via mail. We have included this information in our revised manuscript.

Methods Data Ascertainment Comment #4: "The last sentence stated: 'Staff also contacted these individuals to ensure they received proper follow-up care if needed'. Is follow-up data for those who tested positive available? How many tested positive, how many reached, how many received follow up care? If available, it will be very interesting to include this cascade information in the MS."
Response: We agree with the reviewer that this cascade of information would be very interesting to include. However, VACF did not have this data due to loss of follow-up. One of the main reasons they contacted individuals who tested positive was to help link them to insurance and/or medical assistance programs for treatment, but they do not know whether the individual actually received follow-up care. We have added this information to our revised manuscript.

Methods Data Ascertainment Comment #5: "Please elaborate data management procedure (how data stored and managed)."
Response: All data collected at the VACF screening events are stored and managed in Community TechKnowledge (CTK) Apricot by Social Solutions, a cloud-based client management solution

designed specifically for non-profit organizations. CTK Apricot is HIPAA-compliant and data can only be accessed by authorized users via password-protected accounts. We have added this information to our revised manuscript.

Methods Statistical Analysis Comment #1: “Please include reference(s) for choosing p-value cut off point <= 0.10 for inclusion in multivariate logistic regression.”
Response: We have included a 2017 reference by Ranganathan et al that discusses the use of a more liberal p-value cut-off for inclusion in a multivariable model. All subsequent references have been renumbered to reflect the inclusion of this additional reference.

Methods Statistical Analysis Comment #2: “Can you explain why year of screening was factored in multivariate analysis (Table 3)? Did the data analysis detect any differences in outcomes by year of screening?”
Response: Given that our analysis spans from 2011 through 2017, we included year of screening in our multivariable model as a way to control for any differences that might have occurred over time. When we ran the analyses by year of screening, we did not observe any major differences in the results. We also ran the analyses excluding year of screening from the multivariate analysis and the overall results did not change.

Results Comment #1: “The first sentence of the second paragraph cited Table 2. However, Table 2 seem not have this information. Please add a TOTAL column to table 2 to illustrate information in this sentence.”
Response: We have added a total column to Table 2 to illustrate the information in this sentence per the reviewer’s suggestion. To minimize confusion regarding the numbers and percentages presented in Table 2 with the addition of this total column, we have also revised the table’s column headings and its footnotes.

Discussion Comment #1: “In many cases, attendees of health fairs/events that offer free tests are from low-income and uninsured families and not necessarily a representative sample of the population of interest. A comparison of the study participants’ characteristics with available data on the Vietnamese Americans population will be helpful (e.g. family income, education, place of birth (foreign/US born).”
Response: We have revised the manuscript to include a comparison of our study participants’ characteristics with available data on the Vietnamese American population from the Pew Research Center’s analysis of the American Community Survey (ACS). We have highlighted the differences and similarities between our study population and the general Vietnamese population in the U.S. when comparing characteristics, such as income, education, and foreign-/U.S.-born as suggested by the reviewer.

Reviewer #2:

General Comment #1: “Overall, this paper described serological tests from several thousand people of Vietnamese origin in Southern California and >95% of them were immigrants and >90% of them were older than 40 years old. While it is nice to spread the word that this group has high HBsAg-positivity, this paper is not likely to have a broad appeal because of its limited population and limited data reported here. I wish data were available on what happened to those with positive results on HBsAg. Finding HBsAg-positive immigrants and linking them to anti-HBV drugs to reduce the incidence of cancer is a major priority in the NIH viral hepatitis action plan. Perhaps the authors could frame the paper as implementation science, esp. if they have data on the events themselves (how many came, what % took a test, got results, where was this doctor visit with results, who went for

follow-up and where). That would have more public health impact and would provide rationale for more resources spent testing and linking to care in this community.
Response: We are unable to frame our paper as implementation science since much of the needed information for that type of paper was not collected (VACF was not able to track their participants due to loss of follow-up). What is known is that all screened participants received their results either at a follow-up event (approximately 50-60% attended the follow-up event) or via mail, and significant efforts were taken to link positive individuals to care; we have added this information to our revised manuscript. While the reviewer does make a valid point that this type of approach could have broader appeal, examining the epidemiology of hepatitis B in the Vietnamese community, as we have done in our present analysis, can be very informative as well since strategies to address hepatitis B's burden are often informed by identifying factors associated with its risk. Therefore, we believe this paper does have significant public health impact since it helps provide empirical evidence useful for hepatitis B-related health promotion programs.

Intro Comment #1: "In paragraph 3, when you say Vietnamese American do you mean foreign-born or immigrants? When you say no change over the past 3 decades… are you implying that the # of imported cases of HBV have been stable or are you saying there is transmission on US soil? Why would the incidence of liver CA be expected to drop if there is stable immigration of HBsAg-positives? In fact, if the number immigrating increases, wouldn't the incidence of liver CA in people of Vietnamese ethnicity be possibly increasing?"
Response: Vietnamese American in this paper refers to Americans of Vietnamese ancestry; they include foreign-born individuals and immigrants. Regarding the comment on change over the past decade, the study cited used cancer registry data to examine trends in liver cancer incidence among Asian American subgroups. By including that sentence, we attempted to demonstrate the trend and severity of liver cancer, a malignancy closely tied to hepatitis B, among Vietnamese Americans, especially in comparison to other racial groups/ethnicities. This sentence was also meant to highlight how liver cancer incidence has not improved among Vietnamese Americans, which would suggest that hepatitis B incidence has not improved in this subpopulation as well.

Intro Comment #2: "What else makes Vietnam or Vietnamese unique in terms of HBV. Are HBV control policies different in Vietnam? Are there cultural practices that promote transmission or prevent prevention? Can you make the case better for such a limited study on this group? Do interventions to test and treat HBV in V.A.s need to be different from other Asian immigrant groups?"
Response: We have revised the manuscript to mention the uniqueness of Vietnam and Vietnamese practices with regard to hepatitis B transmission and prevention. We have also revised the manuscript to further comment on the importance of disaggregating the Asian American population in research. This is an issue that has been often cited in literature given that each Asian subgroup is characterized by its own distinct culture, language, and sociodemographic features. We believe this constitutes an important reason for why Vietnamese Americans should be examined separately.

Intro Comment #3: "What do you mean 'updated evaluation?' Was there another identical serosurvey 10 years ago that you repeated?"
Response: In our manuscript, we referenced another study (Nguyen et al, 2015) that also examined hepatitis B in Vietnamese Americans in Southern California using serosurvey data from VACF. That 2015 study used VACF data from 2008 to 2010 whereas ours continues that work using data from 2011 to 2017 (the most recent data at the time of the analysis). Although the 2015 study and our study are methodologically different, both leverage VACF serosurvey data, which is why we referred to ours as an "updated evaluation". We have revised our manuscript to clarify this.

Methods Comment #1: "State the size of the Vietnamese community in the counties where the community events occurred so we can know what % more or less were reached."

Response: We have now included the population of the Vietnamese community in the counties where the screening events took place. This information can be found in the Introduction.

Methods Comment #2: “Where did the testing events occurs?”
Response: The testing events occurred at Orange Coast Memorial Cancer Medical Center in Fountain Valley, California and at various community health fairs and events in the counties of Orange and Los Angeles. We have added this information to our revised manuscript.

Methods Comment #3: “What do you mean complete results? I would not exclude those who at minimum have HbsAg test results.”
Response: “Complete results” referred to participants who had serological testing results for the hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), and total hepatitis B core antibody (anti-HBc). We excluded those who were missing results for any of those tests since all three are needed to properly differentiate those truly at risk of hepatitis B from those previously infected and immune via vaccination. We have revised our manuscript so this is clearer. A unique feature of this analysis is our ability to properly examine hepatitis B risk since we can compare those infected with hepatitis B to those at risk of hepatitis B rather than those simply uninfected as most studies have done. This is why we did not include those who have HBsAg test results, but may be missing anti-HBs and/or anti-HBc test results.

Methods Comment #4: “Ethical considerations such as approval to use the data for research are not mentioned.”
Response: Please see our response for Reviewer #1’s Overall Comment #1 above.

Methods Comment #5: “What assays were used for the HBV serologies as some of the tests are not as accurate and this would reduce confidence in results.”
Response: VACF worked with various commercial laboratories in the Orange County region, but the majority of testing was done using Advia Centaur chemiluminescence immunoassay for hepatitis serology. We have included this information in our revised manuscript.

Results Comment #1: “How many events occurred? How many were tested per event?”
Response: VACF’s main hepatitis screening events were held twice each year with anywhere from 200 to 400 participants in attendance. VACF also provided hepatitis screening services at various community health fairs and events; these had significantly fewer participants (<100). We did not elaborate this in the manuscript because our analysis simply pools the individuals across all events to further our understanding of hepatitis B epidemiology.

Results Comment #2: “Better to say in the results the specific factor. Such as men had increased odds (P=XXX) than just mentioning gender as being associated.”
Response: We have revised Results paragraph 2 per this reviewer’s next comment, which should address this comment.

Results Comment #3: “In the text, don’t give both bivariable and multivariable analysis. Just multi-.”
Response: We have removed our bivariable results from the text and only present the results from the multivariable analysis in our revised manuscript.

Results Comment #4: “What happened to the HBsAg-positives? Were these new diagnoses? Were they linked to care and treatment? Were they screened for cancer? Did you do index testing where their first degree relatives and partners were also tested?”
Response: Those who tested positive for hepatitis B were linked to insurance and/or medical assistance programs for treatment by VACF patient navigators. However, due to loss of follow-up, VACF was not able to track how many actually received the care they need. VACF did not screen for

cancer nor did they do index testing where their first-degree relatives and partners were also tested. However, VACF did encourage family members and partners to get tested. They also helped navigate them to their primary care physicians or to community clinics or other VACF screening events. We have included this information in our revised manuscript.

Results Comment #5: “Did you vaccinate those who were non-immune?”
Response: No, VACF did not vaccinate those who were non-immune. However, efforts were taken to navigate non-immune participants to their primary care physicians to get vaccinations if they have insurance or to community clinics and/or local pharmacies for low-cost vaccinations. We have included this information in our revised manuscript.

Results Comment #6: “How many did not come for results? How many had to be mailed out?”
Response: Please see our response to Reviewer #1’s Methods Data Ascertainment Comment #3 above.

Discussion Comment #1: “Gender differences in HBsAg-positivity are likely due to natural history of virus and host immunity (estrogens, etc.).”
Response: We agree with the reviewer and have now revised the manuscript to reflect this possible biological explanation regarding the gender differences we observed.

Discussion Comment #2: “Would be great to talk about the fairs more as an intervention. What made them succeed? What could make them better? How to link patients to care if they are found HBsAg-pos?”
Response: We agree that it would be great to talk about the fairs/screening events more as an intervention. Therefore, we have included more details about the events in our revised manuscript to provide some contextual information, particularly with regard to VACF’s efforts to link positive patients to care, family members and partners of positive patients to screening services, and at-risk patients to vaccination services. However, because the focus of this particular paper was to evaluate hepatitis B serological data and risk factors among Vietnamese Americans in Southern California, we feel that discussing the screening events beyond this is outside of the scope of our paper.

Discussion Comment #3: “How do we use these data to find HBsAg-pos in America?”
Response: Findings from this study can improve providers’ understanding of hepatitis B risk factors in Vietnamese Americans, which in turn can help them identify those at high risk who need to be targeted for screenings and preventive measures. They also highlight the need for testing before vaccination in order to ensure proper immunity and reduce transmission. We have discussed these points in our manuscript.

Discussion Comment #4: “How should the results on the ‘factors associated with HBV’ be used?”
Response: As mentioned in the paper and in the previous comment, the factors associated with hepatitis B that we found in our study can help in identifying high-risk individuals in the Vietnamese American population who can then be targeted for culturally-tailored hepatitis B interventions. This was discussed in our manuscript.

VERSION 2 – REVIEW

REVIEWER	Thi Thanh Hang Pham Stanford University Asian Liver Center
REVIEW RETURNED	03-Jul-2019

GENERAL COMMENTS	The authors have sufficiently addressed comments from the previous review and I am happy to recommend publishing this manuscript